REMARKS

I. Claim Status

Claims 1-2, 7-22, 27-71, 74-76, 79-105, 111-114, and 120-124 have been canceled without prejudice to further prosecution in a related continuation or divisional application. Claims 3-6, 23, 72-73, 77-78, 106-110, 115-116, 118-119 and 125-126 have been amended. New claims 127-143 have been added. Upon entry of the present Amendment, claims 3-6, 23, 72-73, 77-78, 106-110, 115-119, and 125-143 are pending. All of the pending claims read on the elected species.

Independent claim 1 has been canceled in favor of new independent claim 127, which is directed to a specific embodiment of the present invention. Specifically, claim 127 requires the steps of (i) providing cells that have been transfected or transformed with one or more members of a library of related genes, (ii) growing the cells in vitro in a biological matrix to express the members of the library of related genes, (iii) separating the cells or cell debris thereof from one or more component of interest using centrifugation or filtration in a parallel fashion to provide samples comprising the component(s) of interest, (iv) performing flow injection analysis using electrospray tandem mass spectrometry on the samples from step (iii) to obtain mass-to-charge ratio data for the component(s) of interest. Components of interest are selected from the group consisting of an inorganic ion, a secondary metabolite, a protein binding molecule, a carbohydrate, a carbohydrate binding molecule, an enzyme, an enzyme substrate, a product of an enzyme catalyzed reaction, anucleic acid, and a product of a nucleic acid catalyzed reaction. The claim requires that the component(s) of interest have not undergone chromatographic separation prior to step (iv).

Support for new claim 127 can be found in the specification at p. 12, lines 19-20, p. 15, lines 20-23, p. 17, lines 19-21, p. 28, lines 20-22, and p. 29, lines 14-16, 21-22 (step (i)); at p. 12, lines 28-29, p. 16, lines 1-2, p. 16, lines 32 to p. 17, line 1, p. 17, lines 19-21, and p. 29, lines 27-28 (step (ii)); at p. 3, line 32 to p. 4, line 1, p. 10, lines 2-7, p. 31, lines 5-7, p. 33, lines 7-8, and p. 39, line 33 to p. 40, line 1 (step (iii)); p. 3, lines 26-29, p. 5, lines 2-11, p. 14, lines 20-21, p. 17, lines 20-21, and p. 23, lines 25-27 (step (iv)).

Independent claim 105 has been canceled in favor of new claim 136. This claim is similar to claim 127, except that it is directed to a library of related enzyme encoding genes in step (i) and it includes step (iii) where the cells are contacted with one or more enzyme substrates to initiate formation of one or more products of an enzymatic reaction. Step (iv) requires separating the cells

or cell debris thereof from the product of the enzymatic reaction and/or enzyme substrate using centrifugation or filtration in a parallel fashion to provide samples comprising the product(s) of the enzymatic reaction and/or enzyme substrate(s). Flow injection analysis is performed on the prepared samples to obtain mass-to-charge ratio data for the enzyme substrate(s) and/or product(s) of the enzymatic reaction. This claim requires that the product(s) of the enzymatic reaction and enzyme substrate(s) have not undergone chromatographic separation prior to flow injection analysis (step (v)).

Support for claim 136 can be found in the specification at p. 17, lines 19-21, page 28, lines 20-22 and p. 29, lines 14-22 (step (i)); p. 12, lines 28-29, p. 15, lines 30-31, and p. 17, lines 19-21 (step (ii)); p. 31, lines 5-7 and claim 21 as filed (step (iii)); p. 23, lines 31-32, p. 33, lines 7-8, and p. 39, line 33 to p. 40,line 1 (step (iv)); p. 17, lines 20-21 and p. 23, lines 25-27 (step (v)).

The dependencies of claims 3-6, 23, 72-73, 77-78, 106-110, 115-116, and 125-126 have been amended in view of the cancellation of claims 1 and 105.

New dependent claims 128 and 137 specify that the cells are lysed. (See Spec. at p. 3, lines 32-33, p. 31, lines 10-12 and original claim 13). Dependent claims 129 and 138 specify that the cells are permeabilized. (See Spec. at p. 31, lines 10-12) Dependent claim 130 specifies that the component of interest is obtained from cell supernatant. (See Spec. at p. 3, line 32-33 and original claim 13). Dependent claims 132-133 and 139-140 specify that the cells are either bacterial or eukaryotic. (See Spec. at p. 29, lines 28-32) Claims 134 and 143 correspond to original claim 12. Claim 135 corresponds to claim 115.

Therefore, no new matter is introduced by the amendments and new claims.

II. Rejections

A. 35 U.S.C. § 102(e)

The Office Action has maintained the rejection of claims 1-2, 12-16, 17, 19-20, 22, 72-76, 78, 105, 110, 112-115, 120-121, 123 and 126 under 35 U.S.C. § 102(e) in view of Aebersold et al. (U.S. Pub. No. 2002/0076739 A1). This rejection is respectfully traversed in view of the new and amended claims.

The claimed method differs fundamentally from the method described in the Aebersold et al. reference in that, in the claimed method, what is injected into the mass spectrometer is a complex mixture of molecules left behind after centrifugation and/or filtration to remove cells/cell debris from the samples. Aebersold et al. describe the use of affinity purification to isolate a molecule of interest from a mixture of molecules (e.g., cell protein and biotinylated product). See Col. 12, paragraph 0113. In the Aebersold et al. reference, undesired molecules are eluted from the affinity matrix. The bound affinity labeled molecule is subsequently eluted from the affinity matrix, and this isolated molecule is then subjected to analysis by mass spectrometry. Therefore, Aebersold et al. do not describe performing flow-injection analysis on the samples specified by the claims, i.e., samples generated by steps (i)-(iii) in claim 127 and steps (i)-(iv) in claim 136.

B. 35 U.S.C. § 103 – Aebersold et al. and Siuzdak

Claims 1-2, 12-17, 19-20, 22-26, 72-76, 78, 105, 110, 112-121, 123 and 126 stand rejected under 35 U.S.C. § 103(as) as being allegedly unpatentable over Aebersold et al. and Siuzdak et al. (Siuzdak, Mass Spectrometry for Biotechnology, New York: Academic Press (1992)). This rejection is respectfully traversed in view of the new and amended claims.

The Office Action cites the Siuzdak et al. publication for its reference to "neutral loss" and "parent ion" techniques used on triple quadrupole mass spectrometers employing collision induced dissociation techniques. Applicants respectfully wish to point out that Siuzdak, et al. describe these techniques being applied to fractions collected from preparative liquid chromatography:

> CSF analysis began with preparative liquid chromatography fraction collection. These experiments produced UV data on each fraction to determine any differences between the felines at various points in their sleep cycle. An absorbance was found to be particularly prominent in the CSF of cats that were kept awake for an extended period of time (18 hr).
>
> Even though the compound associated with this absorbance was only present in small amounts, partial characterization was initially obtained by performing exact mass measurements and tandem mass analysis. Using an API III Perkin Elmer SCIEX triple-quadrupole mass spectrometer, electrospray mass analysis on the fractions associated with the differences in the chromatogram produced a significant ion at *m/z* 282. That was determined to be the MH^+ ion, and an exact mass determination on the unknown compound by FAB (Fisons/VBZAB-VSE) was consistent with the molecular formula $C_{18}H_{35}NO$.

P. 120 (emphasis added).

Therefore, the Siuzdak et al. reference describes mass spectrometry analysis on samples purified by liquid chromatography, and not the complex samples generated by the steps of the claimed method. Accordingly, the Siuzdak et al. reference does not cure the deficiencies of the Aebersold et al. reference.

C. 35 U.S.C. § 103 – Aebersold et al. (US No. 2002/0076739), Siudzak et al. , and Weinberg et al. (WO 98/15969)

Claims 1-6, 12-17, 19-20, 22-26, 72-78, 105-110, 112-121, 123, 125, and 126 stand rejected under 35 U.S.C. § 103 over Aebersold et al., Siuzdak et al. (Siuzdak, G. Mass Spectrometry for Biotechnology, New York: Academic Press 1992) and Weinberg et al. (WO 98/15969). This rejection is respectfully traversed in view of the new and amended claims.

The Weinberg et al. reference is cited for its reference to a mass spectrometer that scans an array "faster than 10, 100, or 1000 library elements per second." (Office Action at p. 9) The Weinberg et al. reference describes a scanning mass spectrometer that is used over an array of materials. Gas reactants are introduced which react with the materials on the array. According to this reference, the gas or vapor products are drawn into the ionization chamber of the mass spectrometer for analysis. (WO 98/15969 at p. 6, line 32 to p. 7, line 4; p. 7, line 26-28; p. 15, lines 23-26; p. 20, lines 5-8). Alternatively, only volatile components of liquid or solid phase products are sampled. ("In the case of liquid or solid phase products, volatile components of the products can be sample identically to the gas phase products," p. 15, line 31 to p. 16, line 1) Weinberg et al. do not describe rates of screening for analyzing samples generated from a centrifugation or filtration process (i.e., liquid samples).

Notwithstanding this difference in approaches, both Weinberg et al. and Aebersold et al. take identifiable steps to minimize the complexity of sample components being analyzed by the mass spectrometer. The claimed method necessarily results in a very complex mixture of soluble cellular components being introduced into the mass spectrometer. The samples that are analyzed in the systems described in Weinberg et al. and Aebersold et al. are not complex samples, having undergone either affinity separation or isolation on an array.

The inventors of the claimed invention discovered that the complex samples generated by steps (i)-(iii) of claim 127 and steps (i)-(iv) of claim 136 could be analyzed by mass spectrometry

without further purification to isolate the analytes of interest. Neither Aebersold et al., Siuzdak et al., nor Weinberg et al. provide even a hint that this could be a viable approach for detecting components of interest amongst a background of soluble cellular components.

In view of these differences, which are not suggested by the combination of references cited, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

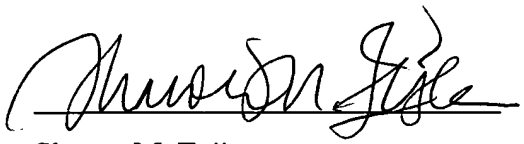
D. 35 U.S.C. § 112, 2nd Paragraph

Claim 12 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for not providing sufficient antecedent basis for the limitation,"said purifying one or more non-column separated samples." This rejection is rendered moot by the cancellation of claim 12.

CONCLUSION

In light of the foregoing amendments and remarks, it is believed that the application is in condition for allowance. Accordingly, reconsideration and favorable action on all claims is earnestly solicited. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set forth below. The Commissioner is hereby authorized to charge any deficiency in fees or credit any overpayment to Deposit Account No. 50-0990.

August 25, 2005

By: 

Sharon M. Fujita
Attorney for Applicants
Reg. No. 38,459

MAXYGEN, INC.
Patent Department
515 Galveston Drive
Redwood City, California 94063
(650) 298-5421 (Telephone)
(650) 298-5446 (Facsimile)
Customer No. 30560